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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,344	09/20/1999	GERHARD SEEMANN	2481.1640	3847

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EXAMINER	
LIETO, LOUIS D	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,344	SEEMANN ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,12,16-21,23,25-30 and 32* is/are pending in the application.

4a) Of the above claim(s) *19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,16-18,23,25-30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 5/15/2006 have been fully considered but they are not persuasive. The amendment has been entered. Claims 11,12,16-21,23,25-30 and 32 are pending. Claims 9,10 and 24 were canceled; claims 16,25,26,28,29 and 32 were amended. Claims 19-21 remain withdrawn.

It is noted that previously withdrawn claim 22 is absent from the present draft of claims and lacks any identifier. Applicant is required to indicate the proper status of previously withdrawn claim 22 in any subsequent response. Failure to do so may result in the issuance of a notice of non-compliance. Claims 11,12,16-18,23,25-30 and 32 are under consideration. The sections of title 35 U.S.C not included in this office action can be found in a previous office action. An action on the merits follows.

Election/Restrictions

This application contains claims 19-21 drawn to an invention nonelected with traverse in response received on 5/14/2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are

canceled, the remaining claims must not be renumbered. It is noted that previously withdrawn claim 22 is absent from the present draft of claims and lacks any identifier.

Claim Rejections - 35 USC § 112

The rejection of claims 9-12,16-18,23-25 and 29-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in view of applicant's cancellation of claims, amendments to the claims and arguments traversing the rejection.

Claims 29, 30 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Response to Arguments

Applicant's arguments filed 5/15/2006 have been fully considered but they are not persuasive fully persuasive in overcoming the previous rejection. Applicant's cancellation of or amendment to the claims, and arguments were persuasive in overcoming the rejection of claims 9-12, 16-18 and 23-25. Applicant argues that the claims drawn to an ex vivo method were enabled at the time of filing. However as previously stated: the specification does not provide any specific guidance on any method of using transgenic mammals cells in *ex vivo* gene therapy. It is noted that applicant has amended claim 29 so that it is limited to a method of increasing

tolerance of a mammal to autologous cells transfected *ex vivo*. However, neither the specification nor the art of record indicates that administering DSG will have any effect on transplants of transgenic autologous cells. This is because the art teaches that using transplants of transgenic autologous cells was a well-known method at the time of filing for preventing rejection. Raper et al. teaches that as early as 1993 it was known that using a patients own hepatocytes, transfected with a retrovirus, in a method of autologous *ex vivo* gene therapy eliminated the risk of rejection {Raper et al. (1993) Cell Transplant. 2:381-400; Abstract}. Ridet concurs, stating that use of adenoviral transfected human adult astrocytes in a method of autologous *ex vivo* gene therapy would obviate immunological rejection and the use of immunosuppressors {Ridet et al. (1999) Hum. Gene Ther. 10:271-280; Abstract}. As previously noted applicant's working examples only deal with models of *in vivo* gene therapy, involving direct administration of retroviruses. The specification does not provide any evidence indicating that DSG would have any effect on the tolerance of a mammal to autologous cells transfected *ex vivo*. Therefore the rejection is maintained for reasons of record, as stated above and in the office actions of 2/10/06.

Rejections based on the second paragraph of 35 U.S.C. 112

The rejection of claims 9-12,16-18,23-25 and 29-32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 102

The rejection of claims 26-28 under 35 U.S.C. 102(b) as anticipated by Smith et al. (Gene Therapy 3:496-502, 1996), is withdrawn in view of applicant's amendments to the claims

The rejection of claims 26-28 under 35 U.S.C. 102(b) as anticipated by Trapnell et al (WO 96/12406, 05-02-1996), is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12 and 16-18, 23, 25-28 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (Gene Therapy 3:496-502, 1996). This new grounds of rejection is necessitated by applicant's amendments to the claims.

Smith et al teaches use of transient immunosuppression with DSG in mice injected intravenously with adenoviral vector carrying the beta-galactosidase gene. Smith et al administered DSG intravenously to the mice at time of the exposure of the adenovirus (see the abstract), and observed that administration of DSG permitted 100 fold increase in expression of factor IX vector after administration of a second adenovirus encoding factor IX vector , compared to a mouse that did not receive DSG (pg. 498, Figure 2, pg. 499, Figure 3). Measurements were taken 35 days after the cessation of DSG treatment. Wherein, the adenoviral

vectors were E1a, E3-deleted vectors (pg. 500, Materials and Methods). Further, Smith et al. teaches that administration of adenovirus vectors frequently induces a neutralizing antibody response that can decrease the efficacy of adenoviral gene delivery (Abstract). Administration of DSG at the time of adenoviral vector delivery prevented the formation of anti-adenovirus neutralizing antibody (Abstract). Smith et al. does not teach only a single administration of a vector encoding a transgene.

Based on the guidance provided by Smith et al. that administration of DSG at the time of adenoviral vector delivery prevented the formation of anti-adenovirus neutralizing antibodies, and the knowledge in the art that administration of adenovirus vectors frequently induces a neutralizing antibody response that can decrease the efficacy of adenoviral gene delivery, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Smith et al. by administering a single dose of an adenoviral vector with DSG.

A practitioner in the art would be motivated to modify the method of Smith et al., in order to maximize the efficacy of single dosage adenoviral gene delivery

The person of ordinary skill in the art would have had a reasonable expectation of success because administering a single dosage of an adenoviral vector with DSG would have been a routine modification in the art at the time of filing.

Claims 11, 12 and 16-18, 25-28 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Trapnell et al (WO 96/12406, 05-02-1996). This new grounds of rejection is necessitated by applicant's amendments to the claims.

Trapnell et al teaches a method of administering to a host concurrently with an adenoviral vector that expresses a therapeutic gene of interest and immunosuppressive agents, such as DSG (see the entire document). Example 3 discloses administration of DSG i.p. once daily beginning the day before administration and continuing for a total of eight days (see page 33, last paragraph). Figure 17 of Trapnell et al shows the human factor IX levels in mice that were administered adenoviral vector expressing factor IX alone or along with DSG or other immunosuppressants. Page 42 (last paragraph) discloses that five weeks after vector administration, no detectable levels of neutralizing antibodies were observed. Trapnell et al also discloses that DSG immunosuppression also allows re-administration of the adenoviral vector (see the last paragraph on page 44 continued on page 45). Claim 1 of Trapnell et al recites a method of gene therapy treatment by administering to a host an adenoviral vector including at least one DNA sequence encoding a therapeutic protein and an immunosuppressive agent and discontinuing administration of said adenoviral vector and said immunosuppressive agent. Claims 10-11, and 14 recite that the immunosuppressive agent is DSG. Claims 19-21 recite that the immunosuppressive agent is administered prior to, at the same time or after the administration of the adenoviral vector. It is noted that while the claims of Trapnell et al. recite re-administration of the vector and DSG, DSG administration is only provided for a certain period of time and then discontinued (see page 33, last paragraph). Trapnell et al. does not teach only a single administration of a vector encoding a transgene.

Based on the guidance provided by Trapnell et al. that administration of DSG prior to the time of adenoviral vector delivery prevented the formation of anti-adenovirus neutralizing antibodies, and the knowledge in the art that administration of adenovirus vectors frequently

induced a neutralizing antibody response that can decrease the efficacy of adenoviral gene delivery, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Trapnell et al. by administering a single dose of an adenoviral vector with DSG.

A practitioner in the art would be motivated to modify the method of Trapnell et al., in order to maximize the efficacy of single dosage adenoviral gene delivery

The person of ordinary skill in the art would have had a reasonable expectation of success because administering a single dosage of an adenoviral vector with DSG would have been a routine modification in the art at the time of filing.

Response to Arguments

Applicant's arguments filed 5/15/2006 have been fully considered but they are not persuasive. Applicant addresses the references of Smith et al. and Trapnell et al. together, so likewise the examiner will address applicant's arguments with a single response. Applicant argues that the goals and object of Smith et al. and Trapnell et al. are different than the goals and object of the claimed invention. Applicant argues that this is sufficient to distinguish the cited art references from the claimed invention. This is not found to be persuasive. As stated above and in the previous actions of 2/10/06, 3/31/05, 7/30/03, 6/24/02, 10/11/01, Smith et al. and Trapnell et al. both provide guidance on the use of the immunosuppressive agent DSG in order to increase tolerance to an adenoviral vector that expresses a therapeutic gene of interest. This goal is the same as that stated by applicant in the reply of 5/15/06 (See page 7). Further, for the purposes of applying art the claims are read in view of what they claim and not in light of limitations only

present in the specification. Applicant argues that the claims have been amended to "single administration of a vector." However, the claims as presently drafted are obvious over the prior art for the reasons set forth above.

No claims allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information

Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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